24. The method according to claim 23 wherein the (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one is combined with a pharmaceutically acceptable carrier.

F3 Cont

REMARKS

Applicants thank Examiner Ford for withdrawing the finality of the January 19, 1996 Office Action. Applicants had responded to that Office Action on July 19, 1996 and filed an Appeal Brief on January 23, 1997.

A. The Claims Now Pending

Amended claim 7 and added claims 23-24 are now pending in this application.

These claims are directed to a method for producing a pharmaceutical composition and to methods for treating patients suffering from HIV infection with (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one substantially free of the corresponding (+) enantiomer. These methods are characterized in that the treatment is associated with a lower cytotoxicity that treatment using the corresponding (+) enantiomer or a racemic mixture of the two enantiomers.

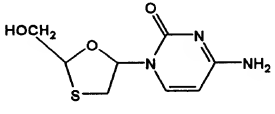
Each of these claims is supported in the application as filed. See, e.g., page 2, lines 4-15;

page 4, lines 1-13; page 5, lines 19-30; and page 29, Table 3. Their entry is requested.

B. Introduction

Before addressing the outstanding rejections, a brief explanation of the technology relevant to the amended claims may be helpful.

In 1988, BioChem's Drs. Bernard Belleau and Paul Ba discovered and produced a class of novel nucleoside analogues that were characterized by a 1,3-oxathiolane pseudo-sugar ring. One member of this class is 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane*:



Each member of this class of nucleoside analogues can exist as two geometric isomers (*cis* or *trans;* also designated β or α, respectively):

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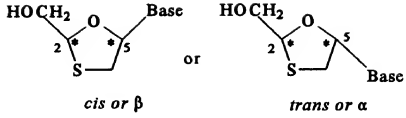
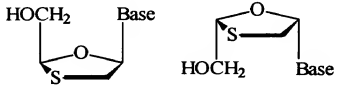
* Other chemical names for this compound are 2',3'-dideoxy-3'-thia-cytidine and 4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.



cis or β *trans or α*

Each of the two geometric isomers of 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane were produced and characterized in Example 7 of BioChem United States patent 5,047,407 ("the BioChem '407 patent"). See, e.g., col. 11, line 50-col. 12, line 32 (Compounds *Cis*-XI and *Trans*-XI).

The oxathiolane ring that characterizes these nucleoside analogues has two chiral centers -- at the 2 and 5 carbons. They are shown by asterisks in the above figures. As a result of this chirality, each of the two geometric isomers can exist as two optical isomers. For example, the *cis* or β geometric isomer may exist as the (+) or d-optical isomer or the (-) or l-optical isomer:



(+) or (d) cis isomer (-) or (l) cis isomer

Optical isomers are also called enantiomers. They rotate plane polarized light in opposite directions -- the (+) and d enantiomer to the right and the (-) or l enantiomer to the left. A racemic mixture or racemate is a 50:50 mixture of the two optical isomers or enantiomers. The separation of a mixture of enantiomers to isolate the individual enantiomers or optical isomers that comprise the mixture is called "resolution". See Corey Decl., paras. 2-3, infra, p. 12.

BioChem produced a racemic mixture of the two optical isomers of cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane in the BioChem '407 patent. See Example 7 -- Compound Cis XI -- col. 12, lines 7-32. See, e.g., Jones Decl., para. 13, infra, p. 12. It designated this racemic mixture "BCH-189". The industry and the patentees of Liotta et al. United States patent 5,539,116 ("the Liotta '116 patent") have adopted BioChem's nomenclature.

Typically, the two enantiomers of a racemic mixture have different biological activities. For example, the compound carvone is an flavor additive. The (-) enantiomer has a spearmint flavor, while the (+) enantiomer has a caraway flavor. See, e.g., Barton Decl., para. 6; Cram Decl., para. 9, infra, p. 12.

The (+) and (-) enantiomers of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane also have

different and unexpected biological activities. Both display similar antiviral activity. See, e.g., Cram Decl. para. 25; Corey Decl., para. 17, infra, p. 12. This is surprising because typically for nucleoside analogues it is the enantiomer that has the same configuration as natural nucleosides, i.e., the D-absolute configuration -- here the (+) enantiomer -- that is primarily biologically active. See, e.g., Trost Decl., para. 37, infra, p. 12:

> "As of February 1990, it was generally believed that most, if not all, biologically active nucleoside analogues would possess the configuration most closely corresponding to nucleosides found in nature [footnote omitted]. This is the "D" or "natural" configuration. For BCH-189, the optical isomer with the D configuration is the (+) optical isomer."

See also Cram Decl., para. 10, infra, p. 12. Surprisingly, the two enantiomers of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane are equipotent.

Even more unexpected, however, is the comparative toxicity of the two enantiomers. The non-native or L-enantiomer -- here the (-) enantiomer -- is much less toxic than the (+) enantiomer. This surprisingly low toxicity, when coupled to its unexpected antiviral activity, results in the (-) enantiomer having a markedly improved therapeutic index over the (+) enantiomer and racemic mixture of the two enantiomers. The (-) enantiomer, also known as EPIVIR™, is now the most prescribed HIV drug in the United States.

The claims now pending in this application recite the characteristics of the (-) enantiomer that render it such a useful treatment against HIV infection -- its low cytotoxicity as compared to the corresponding (+) enantiomer or a racemic mixture of the two enantiomers.

C. The § 112 Rejections

1. Claim 3, 4, and 5: "mixtures"

Claims 3, 4, and 5 stand rejected under 35 U.S.C. § 112, second and fourth paragraphs. Applicants have canceled claims 3, 4 and 5 without prejudice.* This overcomes the rejections.

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* The specification recites a variety of standard, prior art techniques that can be used to prepare the claimed mixtures. For example, chiral HPLC and enzyme mediated enantioselective catabolism are referred to at page 13, lines 10-27.

The specification also exemplifies the results when these enantiomer separation techniques are applied to a mixture of the (+) and (-) enantiomers of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. See, e.g., Example 2: chiral HPLC (page 16, line 20 - page 17, line 30; Example 3: 5' nucleosidase catabolism (page 17, line 31 - page 19, line 7); and Examples 4-5: cytidine deaminase (page 19, line 8 - page 24, line 12). Finally, applicants have demonstrated that the (-) enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one may be produced substantially free of the (+) enantiomer by chiral HPLC (e.g., approximately 100% enantiomeric enrichment. See page 16, line 39).

2. Claim 18: "viral infections"

Claim 18 stands rejected under 35 U.S.C. § 112, first and second paragraph. The Examiner contends that "all viral infections are notoriously resistant to treatment" and suggests that claim 18 be amended to recite treatment of HIV and hepatitis B infections. The Examiner has also objected to the phrase "including man" for being redundant and indefinite as to "which is being treated."

Applicant has canceled claim 18 without prejudice. This overcomes the rejection.

In amending claim 7 and adding claims 23 and 24, applicants have taken the Examiner's comments into account. They have recited only the treatment of HIV infection. They have also recited mammals and omitted the redundant phrase "including man".

3. Claims 21 and 22: "prodrugs" and "esters and salts of esters"

Claims 21 and 22 stand rejected under 35 U.S.C. § 112, first and second paragraphs, for reciting "prodrugs". Specifically, the Examiner contends that the phrase "or a compound which, upon administration to a recipient is capable of providing . . ." refers to prodrugs which are not described or disclosed.

Claims 21 and 22 also stand rejected under 35 U.S.C. § 112, first and second paragraphs, for lack of

description and support for esters and salts. Further, the Examiner contends that salts, esters, and salts of esters of this invention have no established utility.

Applicants have canceled claims 21 and 22 without prejudice.* This overcomes the rejections. In

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* One of skill in the art would readily appreciate how to make and use prodrugs as disclosed within the application as filed (see below). Applicants also continue to believe that pharmaceutically acceptable salts and esters of the compounds of this invention are well defined in scope and are well understood by those of skill in the art.

The application as filed teaches: (1) that pharmaceutical derivatives of this invention may be formed at the functional groups of the base moiety and at the hydroxymethyl group of the oxathiolane ring; (2) that modification of all such functional groups are included in the scope of this invention; (3) that preferred pharmaceutically acceptable esters of this invention are located at the 2-hydroxymethyl of the oxathiolane ring; and (4) that pharmaceutically acceptable salts may be prepared by methods described therein (page 2, line 39-50; page 12, line 22-46). The application further lists preferred esters and salts of this invention (page 2, line 51 - page 3, line 45).

Contrary to the Examiner's assertion that the salts, esters, salts of esters of this invention have no established utility, the application as filed teaches throughout that esterification of compounds of this invention is useful in the treatment of viral infections (page 3, lines 45-49; page 9, lines 9-21; and page 8, lines 29-34). Numerous studies have been published to show the usefulness of esterified compounds to improve the bioavailability, absorption, and stability of a nucleoside (Aggarwal, et al., "Synthesis and Biological Evaluation of Prodrugs of Zidovudine," J. Med. Chem. (1990) 33:1505-1510 and Burr and Bundgaard, "Prodrugs of 5-fluorouracil. v. 1-alkoxycarbonyl derivatives as potential prodrug forms for improved rectal or oral delivery of 5-fluorouracil," J. Pharm. Sci. (1986) 75:552-7 and Balant et al., "Prodrugs for the improvement of drug absorption via different routes of administration," Eur. J. Drug Metab. Pharmacokinet. (1990) 15:143-53) (copies enclosed). The Examiner has provided no evidence to doubt the asserted utility.

amending claim 7 and adding claims 23 and 24, applicants have avoided the objected to language.

In view of these amendments, applicants request that the Examiner withdraw his rejections under 35 U.S.C. § 112.

D. The Art Rejections

All claims stand rejected under 35 U.S.C. § 102 and 103 as unpatentable over the Liotta '116 patent. They also stand rejected for anticipation and obviousness over the BioChem '407 patent. Applicants traverse.

These rejections are inconsistent. On the one hand, the Liotta '116 patent was granted over the BioChem '407 patent. The Liotta '116 patent claims a composition comprising the (-) enantiomer of BCH-189. See, e.g., claims 1-4. In her May 8, 1996 Reasons For Allowance in the application that issued as the Liotta '116 patent, Examiner Tsang said (copy enclosed):

> "US '407 does not enable one skilled in the art to obtain the claimed subject matter without undue experimentation."

On the other hand, claims to the (-) enantiomer of BCH-189 stand rejected in this case over the BioChem '407 patent. In explaining that rejection the Examiner has stated: (page 4):

> "The (-) enantiomer is resolvable from the (±) racemate and is included therein."

To resolve the conflicting positions that the USPTO has taken with respect to the BioChem '407 patent,

applicants' assignee, BioChem Pharma, has concurrently requested that an interference be declared between an application that derives from the application that issued as the BioChem '407 patent and the Liotta '116 patent. As part of that request, applicants have provided the USPTO with extensive, detailed prima facie evidence that, contrary to Liotta's contentions, the BioChem '407 patent does enable the separation of the enantiomers of BCH-189. Some of those Declarations are filed herewith, i.e., the following Declarations Under 37 C.F.R. § 1.132*:

1. Dr. Derek H.R. Barton, Distinguished Professor of Chemistry, Texas A&M University

2. Dr. Elias J. Corey, Sheldon Emery Professor of Organic Chemistry, Harvard University

3. Dr. Donald J. Cram, Saul Winstein Professor (emeritus) of Organic Chemistry, University of California, Los Angeles

4. Dr. Barry M. Trost, Job and Gertrud Tamaki Professor in Humanities and Sciences and Chair of the Department of Chemistry, Stanford University

5. Dr. J. Bryan Jones, University Professor of Chemistry, University of Toronto

Notwithstanding this conflict about the enablement of the '407 patent, the pending claims,

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* Each Declaration will be referred to throughout as "____ Decl., para. ___". For the Examiner's convenience, the Exhibits and Figures (i.e., Corey Decl., para. 3; Cram Decl., paras. 4, 6, 7) are filed herewith in separate volumes with appropriate Tables of Contents.

amended claim 7 and added claims 23 and 24, are patentable over the Liotta '116 patent and the BioChem '407 patent.

The three pending claims are entitled to an earliest effective filing date of May 2, 1990 (UK patent application 9009861.7).* That UK priority application discloses and describes the claimed (-) enantiomer of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and demonstrates its surprising activity and low toxicity, as compared to the corresponding (+) enantiomer. See, e.g., page 2, lines 10-15; pages 23-25. In fact, applicants' UK priority application is the first disclosure that a nucleoside analogue in the non-natural or L-configuration (here the (-) enantiomer) has antiviral activity and is unexpectedly non-toxic as compared to a nucleoside analogue in the natural or D-configuration (here the (+) enantiomer) and the racemic mixture of the two enantiomers.

The UK application also describes and exemplifies the separation of the (-) enantiomer from the racemic mixture BCH-189. See, e.g., Examples 2-4 (UK application 9009861.7, pages 16-22 (copy enclosed)). See also supra, p. 7n.

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* The present application is the United States national stage application of PCT/GB 91/00706, filed May 2, 1991, which application claims priority from British application 9009861.7, filed May 2, 1990.

Subsequent scientific publications have acknowledged the surprising and unexpected activity and low toxicity of applicants' nucleoside analogue. See, e.g., Beach et al., Synthesis of Enantiomerically Pure (2'R,5'S)-(-)-1-[2-(Hydroxymethyl)oxathiolan-5-yl] cytosine As A Potent Antiviral Agent Against Hepatitis B Virus (HBV) And Human Immuno-deficiency Virus (HIV)", J. Org. Chem., 57, pp. 2217-2219 (1992); Chang et al., "Deoxycytidine Deaminase-Resistant Stereoisomer Is The Active Form of (±)-2',3'-Dideoxy-3'- Thiacytidine In the Inhibition of Hepatitis B Virus Replication", J. Biol. Chem., 267, pp. 13938-13942 (1992); Schinazi et al., "Activities of The Four Optical Isomers of 2',3'-Dideoxy-3'-Thiacytidine (BCH-189) Against Human Immunodeficiency Virus Type 1 in Human Lymphocytes", Antimicrobial Agents And Chemotherapy, 36(3), pp. 672-676 (1992)) (copies enclosed with applicants' January 23, 1997 Appeal Brief in this application; see particularly, Appeal Brief, pages 12-14).

1. The Liotta '116 Patent

The Liotta '116 patent has no disclosure of the surprising and unexpected properties of the (-) enantiomer of BCH-189.

In fact, the Liotta '116 patent and its February 1, 1990 parent application (USSN 473,318) does not distinguish at all between the (+) or (-) enantiomer

of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Rather, the Liotta '116 patent and its '318 parent application state that one of the enantiomers of the racemic mixture cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (BCH-189) is "inactive and, therefore, represents a 50% impurity", without saying which one is active. See the Liotta '318 application, page 8, lines 24-25; the Liotta '116 patent, col. 3, lines 45-47. See, e.g., Corey Decl., paras. 16-17:

> "There is no evidence that either the (+) or the (-) enantiomer [of BCH-189] separated from the other was produced by the applicants of the '318 application.
>
> In fact, I found a statement that convinces that the applicants of the '318 application had absolutely no idea of which enantiomer was active because they state at page 8 'the other enantiomer is inactive and, therefore, represents a 50% impurity.' Coates et al. have published that the (-) and (+) enantiomers show approximately equal activity against HIV-1 in their article entitled 'The Separated Enantiomers of 2'-3-Deoxy-3'-Thiacytidine (BCH-189) Both Inhibit Human Immunodeficient Virus Replication In Vitro", Antimicrobial Agents and Chemotherapy, volume 36, pages 202-205, 1992 (EJC13). Had the applicants of the '318 application obtained the (-) and (+) enantiomers separated from the other and tested them, they would have known that both are comparably active against HIV, and they would never have made such an incorrect statement."

See also Barton Decl., paras. 12-14; Cram Decl., paras. 23-25; Trost Decl., paras. 35-36.

Furthermore, the Liotta '116 patent and its '318 parent application suggest by their structural

representations that it was the natural or (+) enantiomer that had the desired anti-HIV properties and conversely that it was the non-natural or (-) enantiomer that was inactive and represented an impurity.* See, e.g., Trost Decl., para. 37.

In fact, the first time that specific reference to the (-) enantiomer of BCH-189 appeared in the Liotta "'318 patent application" was in a February 10, 1993 Preliminary Amendment in the Liotta divisional application (USSN 15,992). At that time, a claim to the (-) enantiomer was added. See February 10, 1993 Preliminary Amendment, Claim 73 (copy enclosed).

In the same Preliminary Amendment, the specification of the Liotta divisional application was

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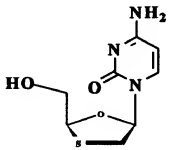
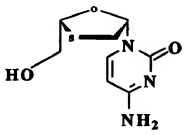
* The conventional structural representations of the natural (here the (+) enantiomer) and the non-natural (here the (-) enantiomer) of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one are:



(+) enantiomer



(-) enantiomer

The Liotta '318 parent application and '116 patent use only the former structure. See, e.g., the Liotta '318 parent application, Figure 4, structure 14 and page 11, lines 7-20; the Liotta '116 patent, Figure 4, Structure 14 and col. 4, lines 47-58.

amended to recite, for the first time, a method to resolve the racemic mixture of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one into its enantiomers (Preliminary Amendment, page 1):

> "For example, the alkyl ester of the β-isomer of BCH-189 can be resolved into its (+) and (-) enantiomer by treatment with pig liver esterase, porcine pancreatic lipase, or subtilisin, by methods described in detail herein"

Yet, even this Liotta divisional application still made no distinction between the (+) and (-) enantiomers and failed to appreciate the special and unexpected properties of the (-) enantiomer.

Liotta contends that the '318 application describes a "second" enzymatic method of resolving BCH-189. See December 22, 1995 Response, Paper No. 25, pages 5-6 (copy enclosed). Liotta points to page 14. In the '318 application, that page recites (i.e., before the February 10, 1993 Preliminary Amendment):

> The protecting group R in 1 can be selected to provide protection for the corresponding alcohol until the final step in the synthesis is carried out (deprotection of 5 to form 6). Additionally, the protecting group can be selected, if desired, to provide an additional recognition site for an enzyme to be used later in an enantio-selective hydrolysis reaction. Any group that functions in this manner may be used. For instance, alkyl, silyl, and acyl protecting groups or groups that possess substantially the same properties as these groups can be used."

Liotta's reliance on this paragraph and particularly the term "later" on line 8, is misplaced. See Trost Decl., paras. 44-46:

> "Read in the context of the '318 application, this language elaborates on the previous paragraph in that application, which discusses the synthesis of racemic BCH-189, and states what roles the "protecting group R" can serve -- for protection until the final step or for an enzyme recognition site for an enantioselective hydrolysis reaction. This language simply states that a "protecting group R" can be chosen for compound 1 at the beginning of the synthesis so that an enzyme can be used 'later' -- i.e., after compound 1."
>
> "Although there are several places after compound 1 that an enzyme could be used to achieve resolution, the application indicates the 'later' use of an enzyme to be at the oxathiolane lactone intermediate. This route to enantiomerically enriched BCH-189 subsequently proved to be ineffective as noted above."
>
> "In reviewing the '318 application, one of ordinary skill in the art would understand that Drs. Liotta and Choi were describing and claiming as their invention a method of making enantiomerically enriched BCH-189 that involved the use of an enzymatic hydrolysis on an intermediate in the synthesis. They would not understand that Drs. Liotta and Choi were describing and intending to claim as their invention the routine method of preparing enantiomerically enriched BCH-189 using enzymatic resolution of racemic BCH-189, or the (-) enantiomer of BCH-189 in enantiomerically enriched or pure form."

Accordingly, the Liotta '116 patent can not render unpatentable the pending claims. Each of those claims requires that the recited HIV treatment be associated with a lower cytotoxicity than treatment using the corresponding (+) enantiomer or a racemic mixture of

the two enantiomers. The Liotta '116 patent has no such teaching or suggestion. At best, it teaches away from the claimed invention.

2. The BioChem '407 Patent

The BioChem '407 patent also has no recognition that the (-) enantiomer of BCH-189 has a lower cytotoxicity than the corresponding (+) enantiomer or a racemic mixture of the two enantiomers. As a consequence, the pending claims are patentable over the BioChem '407 patent.

E. Conclusion

Applicants believe that they have addressed all the Examiner's rejections and that no outstanding rejections remain. Applicants request that the Examiner reconsider the rejections in view of the amended and added claims. Their allowance is requested.

Should the Examiner believe that anything else is needed or would be helpful, he is asked to telephone to the undersigned.

I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON D.C 20231, on

10/16/97

James F. Haley Jr.

Name of person Signing

J. F. Haley Jr.

Signature of Person Signing

Respectfully submitted,

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